



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

May 3, 1999

SUBJECT: DDVP (084001 ): Response to AMVAC letter of 1/19/99 related to EPA's basis for concern for potential developmental neurotoxic effects, and revised HED testing recommendations.  
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Summary

The purpose of this memorandum is to provide a written response to the 1/19/99 AMVAC letter regarding additional information obtained with respect to a study by Mehl et al. (1994) which was used to support concern for potential developmental neurotoxic effects of DDVP, including both a recommendation for testing and maintaining an FQPA factor of 3. These issues were also recently reviewed by the SAP on July 30, 1998 which provided comments (US EPA, 1998).

In response to AMVAC's concerns and SAP's comments, HED maintains that its concerns are justified, and is revising its testing recommendation to ask that SRRD request that the registrant conduct a developmental neurotoxicity study in rats.

To consider the comments of AMVAC and the SAP, and to help draft the HED response,

a meeting was held on March 29, 1999. In attendance were William Burnam, Ray Kent, Susan Hummel, Karen Hamernik, Joycelyn Stewart, and William Sette.

#### I. AMVAC letter Additional Details regarding Mehl et al. 1994

First, it should be noted for the record that this letter represents assertions by AMVAC regarding this study and are not the direct representations of the study authors. EPA should consider direct contact with the study authors to substantiate these assertions if necessary for a regulatory conclusion. In their letter of 1/19/99, AMVAC presents 6 details of this study, in brief:

- that they used the subcutaneous dosing route(not mentioned in the publication);
- that the animal receiving 15 mg/kg had clinical signs;
- that an animal receiving 20 mg/kg had severe signs and was not studied further;
- that 2 animals dosed with 30 mg/kg had clear signs and different dosing regimens;
- that animals were treated over a period of years, but reported in this one study; and
- that the study was not conducted under GLPs, a demonstrable quality assurance program, and they could not provide laboratory records for the registrant.

On the basis of these details, they conclude:

"it is totally inappropriate to use this data as a basis for a regulatory decision. It is arbitrary for the Agency to request us to repeat a study when the limited findings are at near lethal range from an exposure route wholly inappropriate for a pesticide. In particular, the allocation of an additional x3('FQPA')[sic] is not defensible where no selective fetal toxicity is demonstrated."

#### HED RESPONSE

First, AMVAC mis-states the FQPA regulatory requirements. It is inappropriate to refer to "the allocation of an additional x3 ('FQPA') factor" because the law requires that a factor of 10 be maintained unless reliable data can support another factor. The FQPA committee in fact, reduced that factor to 3 based on the available required studies, which did not show indication of increased susceptibility, and because a study to resolve the uncertainties raised by the Mehl et al. study was requested by EPA.

Second, the lack of GLPs and quality assurance are common with studies conducted in academic laboratories throughout the world, and do not, in themselves, invalidate the findings, or make them unusable by EPA.

Third, the fact that the dosing in the study was subcutaneous does not invalidate it in terms of identifying any potential hazard. AMVAC has offered no suggestion as to why this would make a difference for DDVP in terms either of general toxicity or of causing this effect.

Fourth, the relatively large size of the doses used, and the need to use 2x daily doses were generally clear from the paper. With the 15 mg/kg dose, the authors described the clinical signs in the dam as slight. While reasonable parties may disagree about what doses ought to be used, and acknowledging that one daily dose is the standard in most developmental studies, the simple presence of clinical cholinergic signs in the dam does not clearly relate to brain hypoplasia in the offspring. This brain effect was not seen with the more potent cholinesterase inhibitor soman in

the Mehl et al. study, which lead the authors to speculate that this effect is not related to cholinesterase inhibition *per se*.

EPA would acknowledge that this is a limited study, but that these details do not invalidate the findings or the uncertainty they raise. More importantly perhaps, it bears repeating that while this is the only guinea study of DDVP that addressed this effect, the literature on this effect includes several studies of trichlorfon, which is metabolized to DDVP, and generally regarded as the active metabolite with respect to its neurotoxic effects as a cholinesterase inhibitor. Independent of this mechanism, these 2 organophosphates are close structural analogues of one another. The published literature noted by Mehl et al. (several studies in at least 3 different laboratories) on trichlorfon grew out of episodes with domestic animals treated with it, in whom the effect of reduced brain size was first reported. Thus, the concern is broader for trichlorfon and this effect from trichlorfon and its metabolite (DDVP) may be caused by one or both moieties.

## II. SAP Comments and concerns

The SAP raised the issue of whether the limitations in the Mehl et al. study should be used to justify additional research, and questioned whether a new guinea pig study would have benefit of a sufficient body of historical data to provide a context for evaluation. They also expressed concern at the lack of cognitive testing for DDVP and the implications of its absence for reducing the FQPA factor (one member suggesting that the 10x be maintained).

Despite the reservations about the Mehl et al. study, the SAP recommended that the Agency further investigate whether:

If the study were conducted according to an acceptable experimental design, would the effects be replicated? and

Is the guinea pig an acceptable test species to predict the risk of human developmental effects?

In addition, they noted "the absence of any developmental neurotoxicity studies and reiterated the importance of exploring effects on higher brain functions (e.g., cognition, memory, and learning) that may result from lower doses than those affecting brain weight."

For all organophosphates, SAP has repeatedly also expressed concern for developmental neurotoxicity, recommending that all agents that kill insects by neurotoxic mechanisms undergo such testing. EPA has also expressed its general agreement with these concerns and the broader requirement of such studies is under active consideration and review to modify its data requirements.

## HED Response

The guinea pig has been used for studies of the impact of agents on development for a variety of materials. A MEDLINE search identified 17 papers on developmental toxicity in guinea pigs, including studies on methylmercury, 1,3-butadiene, carbon monoxide, and acrylamide.

Thus, there is a literature on this species in relation to developmental toxicity. Second, it may be noted that the small litter size of this animal in relation to rats and rabbits and the longer gestation time make it MORE similar to humans than these other species. Nonetheless, there is far less data on this species than in rats or rabbits.

Second, while guinea pigs have also been used in some behavioral studies, they are also a much less common test species than the rat with respect to behavioral tests, including cognitive function studies, and with respect to developmental neurotoxicity studies.

While it has been reported that rats given 100 mg/kg of trichlorfon on selected days of gestation did not show brain lesions, no further details are reported (Berge et al., 1986). There is a chance, then, that rats may not display this effect.

On the other hand, the use of the rat and the standard guideline for the developmental neurotoxicity study allows for a much broader evaluation of both the neuropathology of the pre-natally (and potentially post natally) exposed animals, and for much more extensive tests of behavior, including detailed observations, development of motor activity, auditory startle habituation, and tests of learning and memory.

Considering these factors, it is recommend that the request for a guinea pig study be withdrawn, and that a developmental neurotoxicity in rats be requested.

## References

Berge GN, Nafstad I, and F Fonnum. 1986. Prenatal effects of trichlorfon on the guinea pig brain.

Mehl A, Schanke TM, Johnsen BA, Fonnum F. 1994 The effect of trichlorfon and other organophosphates on prenatal brain development in the guinea pig. *Neurochem Res* 19(5): 569-74.

US EPA. 1998 FIFRA Scientific Advisory Panel. 7/30/98. A Set of Scientific Issues Being Considered by the Agency in Connection with DDVP(Dichlorvos) Risk Issues. pp 14-26